Letter to the Editors

Circles of Hell: researchers' nightmare or laps of the regulatory pentathlon?

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I doubt that personal spats between foot-soldiers will further solutions to the research governance problems unmasked by Paul Stewart and myself in the BMJ last year [1]. Almost 1 year on, I believe progress is unlikely until the monarchs with the money at grant foundations concede that their largesse is being wasted and take sanctions against the robber barons among regulators. What follows therefore is a mere exhibition joust, aimed mainly at our common and worst foe, R&D; their incompetence and intimidation were not fully manifest at the time of my article [2], but were exposed by the unanimous obloquy directed at them during the meeting of National Institute of Health Research Senior Investigators in April at the Wellcome Trust (<http://www.nihr.ac.uk/files/pdfs/DismantlingBarriersWorkshop.pdf>).

First, however, I thank Frank Wells for his concerns on behalf of my patients. His wish, in retirement, to 'look after the interests' of patients referred for specialist care chimes with the self-appropriated mission of the lay body, National Research Ethics Service (NRES), to protect – presumably from their doctors – the well-being of patients. I am not sure that my appreciation is shared by the patients who have waited a year, and counting, to participate in trials that improve their standard of care; or by the volunteers and benefactors of the British Heart Foundation, whose hard-earned pounds and pence now pay staff to fell trees for red tape, rather than advance medical knowledge and practice. The Declaration of Helsinki, enshrined in the International Conference on Harmonization Good Clinical Practice (GCP) guideline, states that 'The rights, safety, and well-being of the trial subjects are the most important considerations and shall prevail over interests of science and society'. There is nothing in the Declaration, guideline, or Medicines Act that accords research ethics committees (RECs) preference shares in this principle. Not only would it be strange if the part-time, retired and lay constituency meeting once or twice a month were better able to look after patients' interests than physicians used to implementing GCP every day in the clinic; disasters like Northwick Park are most likely to happen precisely when

supposedly expert investigators bet on risk prediction (or nonprediction!) by well-meaning amateurs.

Of course RECs are a mark of a civilized society. The better ones recognize that healthy research and clinical excellence go together, and that the REC's role in most projects is minimalist facilitation. Wells is wrong that I am ignorant of ethics committees, having sat on, or chaired, these for many years – but not since meetings expanded towards day-long affairs with each application an 80-page booklet. These self-inflicted workloads are the reason for long delays before applicants may have their applications heard – which disingenuously are not counted in the 'efficiency' record of the committees. Either applicants write the 80 pages and wait for R&D to sign before requesting a date, which is often 2 months off, or they request a date and then have 4 days to write 80 pages and plead with R&D to sign. Wells may think the system is sorted, but the 80 pages, and hundreds of different boxes that prevent pasting from the protocol, are what deter the majority of busy real clinicians from making it to first base as would-be clinical researchers. At one of this year's prestige competitions for clinician scientists and senior research fellows – the cream of aspiring career clinical academics – only one out of the 30-strong short-list proposed a clinical trial: hardly the expected return on investing £1.3 billion of taxpayers' money into translational medicine.

Where Wells and I are in agreement is that the 'pervading . . . bureaucracy' of ethics committees is well-organized purgatory compared with the lawless inferno of 'overwhelming deficiencies of the R&D Governance process, with which the NHS has lumbered itself'. This process, he 'freely acknowledges, is a nightmare.' What surprises me, however, is his failure to mention that Dante would find NRES and national R&D occupying literally neighbouring levels or circles – at the National Patient Safety Authority in Maple Street; yet Dr Wells' letter is a rare, if not unique, public acknowledgement by RECs of their neighbour's sins. Indeed, the selective choice of items which Wells (and RECs in general) deem relevant to the ethics of research undermines claims to be the moral guardians of our

patients. While I am sorry to have offended a former partner in the mission of expanding Clinical Pharmacology training posts, campaigns against the lethal combination of nightmare and apathy are likely to take few prisoners. As UK Clinical Trials sink, along with UKPLC itself of which Pharma was one of few bastions, Wells' sorrow at my criticisms and irritation at my patient information sheets (PIS) seem as relevant as complaints from the deckchair attendants on the Titanic (by the way, are RECs unaware that investigators *talk* to our patients, who find the PIS much too long and legalese?). Even if the REC process were paradise and perfection, RECs share care for the whole patient, and cannot take satisfaction, as black humour has it on the ward, from the patient dying with normal (ethical) electrolytes.

Indeed, obtaining REC approval is but one major discipline within a whole pentathlon (heptathlon in Scotland) of multiple jeopardy. In this sport, the trial protocol (there can only be one per trial, surely?) is written in five different ways for five bodies, dispatched supposedly in parallel over the five sets of hurdles, but in reality these are set up in random series. The British Heart Foundation (BHF)-funded PATHWAY programme of three trials in eight centres, outlined in my article, is now more than 18 months on from award. Yet only one out of the three trials has been approved in any of the centres; I have been waiting 6 months for local R&D approval of the second trial. Most centres in Scotland still have no approvals; here there is a national review layer of red tape before R&D even starts (I believe in a forlorn hope of Edinburgh talking to Glasgow), and a thick layer of obstinacy thereafter. One recent rejection cites a failure of the Medicines and Healthcare products Regulatory Agency (MHRA)-approved label to mention that patients should not stop their medicine (a 30-year old drug prescribed to millions every day in clinic) without consulting their doctor. Another R&D director blames his delay in approving the first PATHWAY trial on the absence of paperwork for the other PATHWAY trials. Not only is this other paperwork irrelevant to the first, but it should in any case have been received months ago through the NRES's vaunted 'co-ordinated system for gaining NHS permissions (CSP) which streamlines the processes by which NHS Trusts provide permission' (<http://www.nres.npsa.nhs.uk/applications/apply/research-governance-framework/#NHSRDCoordinated>). In London, R&Ds have assumed an additional role of demanding protection money against unforeseen and undocumented costs to the Teaching Trust of participating in word-class research, e.g. £1.5 M at one centre, when the whole BHF grant for eight centres was £1.8 M. Such R&Ds are eyeing with greed and rosy spectacles the pots of money distributed through the new pentathlon discipline of comprehensive local research networks. In Scotland, where the equivalent money is in a less accessible or identifiable location, R&D just bluster, delay or say no. Their Chief Scientific Officer suggested that we should not have applied to the

BHF until R&D costing and approval for all studies had been obtained – in about 2012 at the present rate, when the BHF would promptly reject their inflated demands. This would all be comic, if not so tragic and a heinously unethical use of taxpayers' and charitable money at a time when many of those who paid the money now find themselves out of a job.

R&D is paralegal, received no mention in the Medicines Act [3], and is not subject to any standardized time constraints or process. The Department of Health itself now acknowledges that 'in too many NHS Trusts, the R&D Departments add unnecessary burdens to the ongoing management of research. Many complain that this situation is hindering not facilitating research' (<http://www.nihr.ac.uk/files/pdfs/Implementation%20Plan%204.1g%20Bureaucracy%20Busting.%20NIHR%20Research%20Support%20Services.pdf>). In one institution known to Dr Wells, fear of closure by the MHRA inspectorate led to creation of a star-chamber-like GCP committee, whose members, with little or no experience of designing and managing clinical trials, assume the Trust's or Sponsor's power to summarily suspend low-risk peer-reviewed charity-funded research (despite expert, international advice), and to sanction serious disciplinary threats against senior staff perceived out of line. . . . And this in the centennial year of one ancient University's foundation by scholars fleeing summary justice in another! Today's regulatory climate discourages clinicians wishing to translate research from bench to bedside, with a consequent year's delay in starting experiments; while those embarked on clinical research are encouraged to keep their heads down rather than risk their trials, their jobs or their liberty.

Doubtless some find my complaints annoying. Doubtless I annoyed many in 2007 when I found myself an unlikely champion of the oppressed junior doctors [4]. No personal offence is intended, and I apologize for any that is taken. Much greater apology would be expected by the large number of helpless patients and doctors if no one in a senior position were trying to overturn barriers to their participation in life-saving research. Best of all would be if Dr Wells, from the safety of retirement, will work with me to expose and overcome the real opponents to ethical research. His main love, other than RECs, has been fraud busting. May not wrongful proscription of research, or selective reporting of audits to MHRA, be as harmful as fraudulent description? To protect the punctuation in the PIS, or the investigator in distress – there is a real ethical dilemma!

Competing interests

None declared.

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